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12. 02. 04

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INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

MAILED 13 FEB 2004
WIPO PCT

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**1265/Del/02** dated* ***16th December 2002.***

Best Available Copy

Witness my hand this 19th day of January 2004.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

(S.K. PANGASA)
Assistant Controller of Patents & Designs

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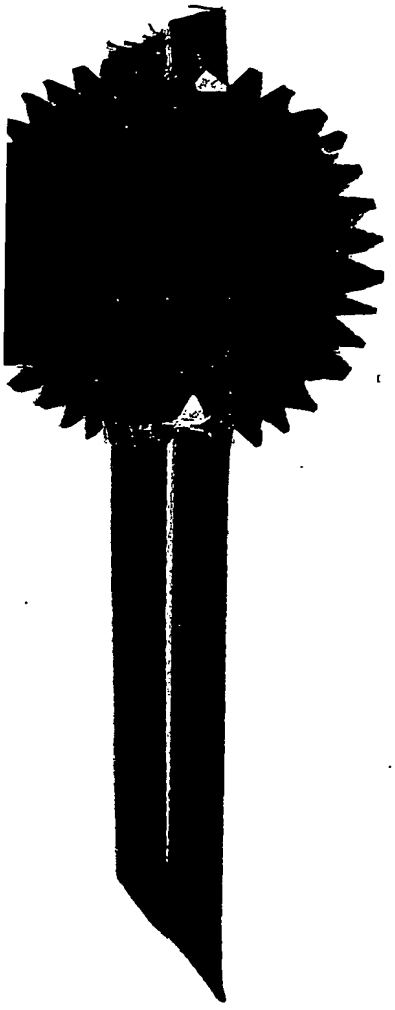


1265-02

16 DEC 2002

Govt. of India Patent Office New Delhi Received Rs. ... in cash. Che ue/M.O. ... O/D.D. on 16 DEC ... Vide Entry No. ... in the Register

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"RABEPRAZOLE CALCIUM"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. MOHAN PRASAD

c. NEELA PRAVEEN KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representative of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

FORM 2 1265-02

16 DEC 2002

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

RABEPRAZOLE CALCIUM

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The invention also relates to a process for preparing rabeprazole calcium, which comprises contacting rabeprazole freebase or its sodium salt with calcium salt of an acid in a suitable solvent, to form rabeprazole calcium, wherein the process is carried out in the presence of a base whenever rabeprazole freebase is used.

Further aspects of the invention include a method for treating or preventing gastrointestinal ulcers which comprises administering to a patient in need thereof an effective amount of rabeprazole calcium, and a pharmaceutical composition for use in the treatment or prevention of gastrointestinal ulcers that comprises an effective amount of rabeprazole calcium along with pharmaceutically acceptable excipients.

Detailed description

The term "rabeprazole calcium" as used herein means any salt comprised of rabeprazole anions and calcium cations. For instance, solid as well as dissolved forms are included as are crystalline and amorphous forms.

Further, the term "rabeprazole calcium" encompasses stoichiometric as well as non-stoichiometric ratios of rabeprazole anion and calcium cation. The ratio of rabeprazole to calcium is not required to be 1:1 in order to be termed rabeprazole calcium. Rabeprazole calcium is preferably formed as a salt having a 2:1 molar ratio between rabeprazole anion and calcium cation (i.e., rabeprazole hemicalcium). Rabeprazole hemicalcium may be formed even when an excess of rabeprazole or an excess of calcium salt of an acid is used in the salt formation.

Rabeprazole calcium obtained in both crystalline and substantially amorphous forms is non hygroscopic. Amorphous form may be advantageous in comparison with the crystalline form as it is obtained in a finely powdered form with better solubility properties.

Rabeprazole calcium and particularly rabeprazole hemicalcium may exist in an anhydrous and/or solvent-free form, or as a hydrate and/or a solvate. The hydrates and alcohol solvates of rabeprazole calcium, especially hydrates and alcohol solvates of rabeprazole hemicalcium, form another aspect of the invention. In particular, methanol solvate of rabeprazole hemicalcium forms yet another aspect of the invention.

Suitable solvents for carrying out the process include water, alcohols such as methanol, ethanol, propanol, or isopropanol, ketones such as acetone or methyl isobutyl ketone, esters such as ethyl acetate, ethers such as dioxane or tetrahydrofuran, nitriles such as acetonitrile, dipolar aprotic solvents such as dimethylsulfoxide or dimethylformamide, hydrocarbons such as hexane or toluene and mixtures thereof.

Preferred solvents are those wherein the reactants are more soluble than the rabeprazole calcium product. In this way, the salt forming reaction is accompanied by spontaneous precipitation of the produced calcium salt out of the solution. Examples are water, alcohols such as methanol, ethanol and isopropanol, esters such as ethyl acetate, and hydrocarbons such as toluene.

The precipitated calcium salt may be isolated in a solid state by conventional methods such as filtration or centrifugation, optionally followed by washing and/or drying and may be purified by crystallization, for example at elevated temperature in an appropriate solvent, for example water, an alcohol such as methanol, or a ketone such as acetone.

The above described methods allow for the production of rabeprazole calcium in a substantially amorphous form when water alone is used as the solvent. Rabeprazole calcium is obtained in crystalline form when organic solvents are used.

Rabeprazole calcium is a useful proton pump inhibitor and an antibacterial, and thus can be used to treat any condition that would be benefited by administration of a gastric acid secretion inhibitor. In particular, rabeprazole calcium can be used for healing of erosive or ulcerative gastroesophageal reflux disease (GERD); maintenance of healing of erosive or ulcerative GERD; healing of duodenal ulcer; treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome, by administering an effective amount of the salt to a patient in need thereof. The specific form of rabeprazole calcium to be used is not particularly limited and specifically includes rabeprazole hemicalcium.

The salt can be administered by any suitable route including oral, parenteral or transdermal. The "patients" intended to be treated include human and non-human mammals.

Process for Preparing Rabeprazole Calcium in Crystalline Form

EXAMPLE 1

2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methylsulfinyl]-1*H*-benzimidazole, hemicalcium salt, methanol solvate

Sodium hydroxide flakes (2.8g, 0.07m) were dissolved in methanol (175ml). To the above solution was added rabeprazole base (25 g, 0.0696 m) at 15-20°C and stirred for 15 minutes. Calcium acetate (7.7g, 0.048m) was added to the resulting solution. The reaction mixture was stirred for 30 minutes and the solution filtered to remove the undissolved particles. The filtrate was stirred for 14 hours at room temperature, the solid that separated out was filtered, washed with methanol and dried under vacuum at 40°C to give white crystalline rabeprazole calcium (23.2g).

Assay (by HPLC) : 99.0%, Water (w/w) : 7.56%, Ca content (w/w) : 5.41%

^{1}H- HMR (DMSO-d_6, δ, ppm); 1.94-2.02(m, 2H), 2.08(s, 3H), 3.18(s, 3H), 3.25(s, 3H), 3.51(t, 2H), 4.09 - 4.13(t, 2H), 4.47(dd, 1H), 4.65(dd, 1H), 6.88 - 6.97(m, 3H), 7.49- 7.52(m, 2H), 8.30(d, 1H).

XRD, IR and DSC spectra are as shown in Figure I II, & III respectively.

EXAMPLE 2

2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methylsulfinyl]-1*H*-benzimidazole, hemicalcium salt, methanol solvate

Rabeprazole sodium (25g, 0.0656 m) was dissolved in methanol (175ml) at room temperature. Calcium acetate (7.7g, 0.048m) was added to the above solution. Initially the solution becomes clear. The clear solution was stirred for 14 hours at room temperature, the solid that separated out was filtered, washed with methanol and dried under vacuum at 40°C to give 23.0g of white crystalline rabeprazole calcium.

Assay (by HPLC) : 99.03%, Water (w/w) : 4.93%.

XRD, IR, NMR and DSC spectra are similar to those for example 1.

Claims:

1. A calcium salt of rabeprazole.

2. The salt according to claim 1, which is rabeprazole hemicalcium.

3. The salt according to claim 1 or 2, which is in a crystalline form.

4. The salt according to claim 3, which is an alcohol solvate.

5. The salt according to claim 4, which is a methanol solvate.

6. The salt according to claim 1 or 2, which is in a substantially amorphous form.

7. The salt according to claim 1 or 2, which is hydrated.

8. A process for preparing rabeprazole calcium, which comprises contacting rabeprazole freebase or its sodium salt with calcium salt of an acid in a suitable solvent, to form rabeprazole calcium, wherein the process is carried out in the presence of a base whenever rabeprazole freebase is used.

9. The process according to claim 8, wherein the calcium salt of an inorganic acid is used.

10. The process according to claim 9, wherein the calcium salt is selected from the group consisting of calcium chloride, calcium nitrate, calcium sulphate, calcium phosphate, calcium carbonate, and calcium dihydrogenphosphate.

11. The process according to claim 8, wherein the calcium salt of an organic acid is used.

12. The process according to claim 11, wherein the calcium salt is selected from the group consisting of calcium oxalate, calcium acetate, calcium lactate, calcium succinate, calcium citrate, and calcium tartrate.

23. The process according to claim 8 or 18, wherein the hydrate of rabeprazole calcium is obtained.

24. A method for treating or preventing gastrointestinal ulcers, which comprises administering to a patient in need thereof an effective amount of rabeprazole calcium.

25. The method according to claim 24, wherein rabeprazole calcium is used for healing of erosive or ulcerative gastroesophageal reflux disease (GERD); maintenance of healing of erosive or ulcerative GERD; healing of duodenal ulcer; or treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

26. The method according to claim 24, or 25 wherein rabeprazole hemicalcium is administered.

27. A pharmaceutical composition for use in the treatment or prevention of gastrointestinal ulcers comprising an effective amount of rabeprazole calcium and pharmaceutically acceptable excipients.

28. The pharmaceutical composition according to claim 27, wherein rabeprazole hemicalcium is used.

29. The pharmaceutical composition according to claim 27, or 28 wherein a crystalline form of the rabeprazole calcium is used.

30. The pharmaceutical composition according to claim 29 wherein an alcohol solvate of the rabeprazole calcium is used.

31. The pharmaceutical composition according to claim 27, or 28 wherein a substantially amorphous form of the rabeprazole calcium is used.

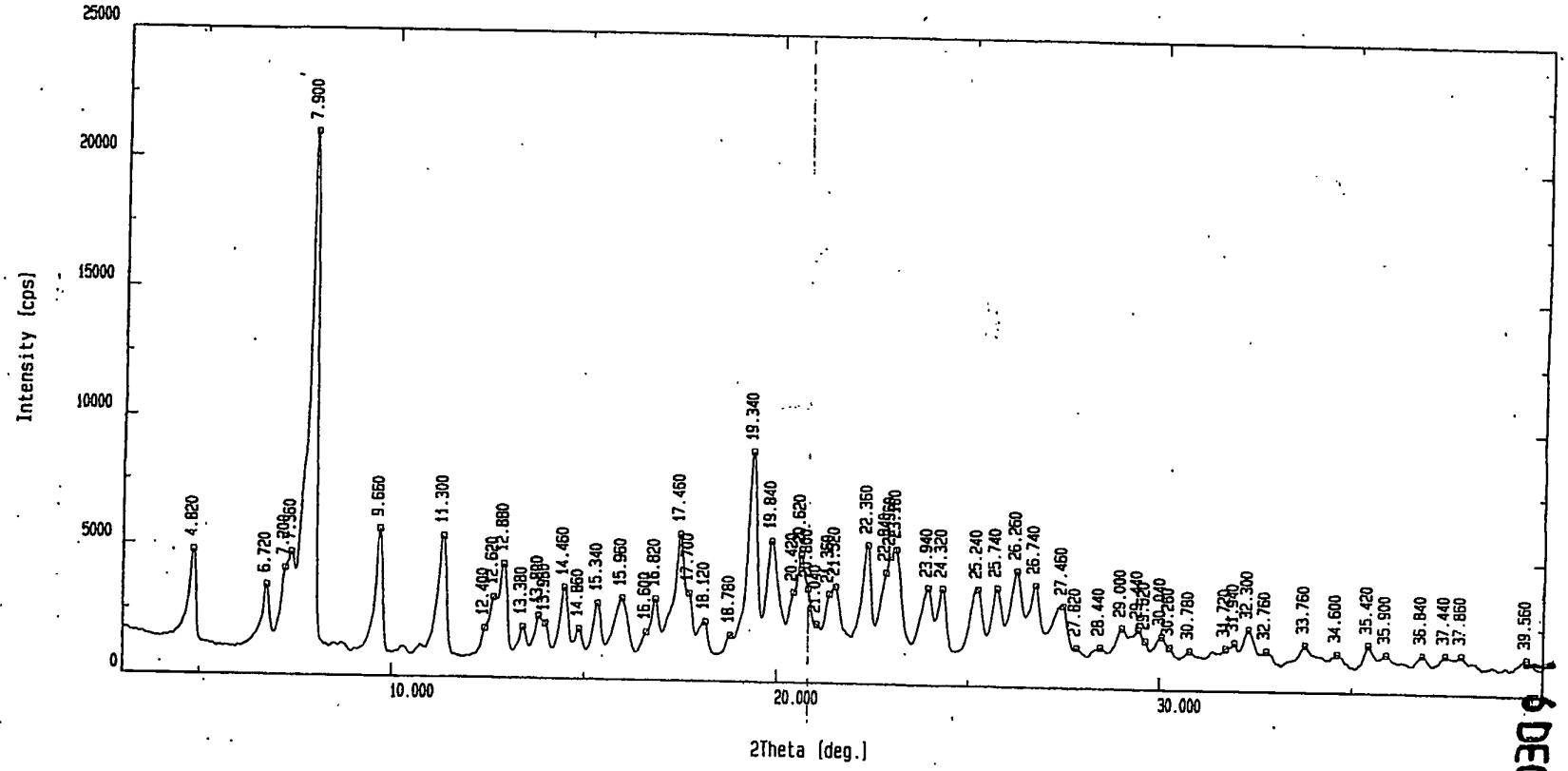
ABSTRACT

The present invention relates to a novel calcium salt of rabeprazole, to processes for preparing it, pharmaceutical compositions of the salt and to its use in treatment or prevention of gastrointestinal ulcers.

Application No.

DUPLICATE

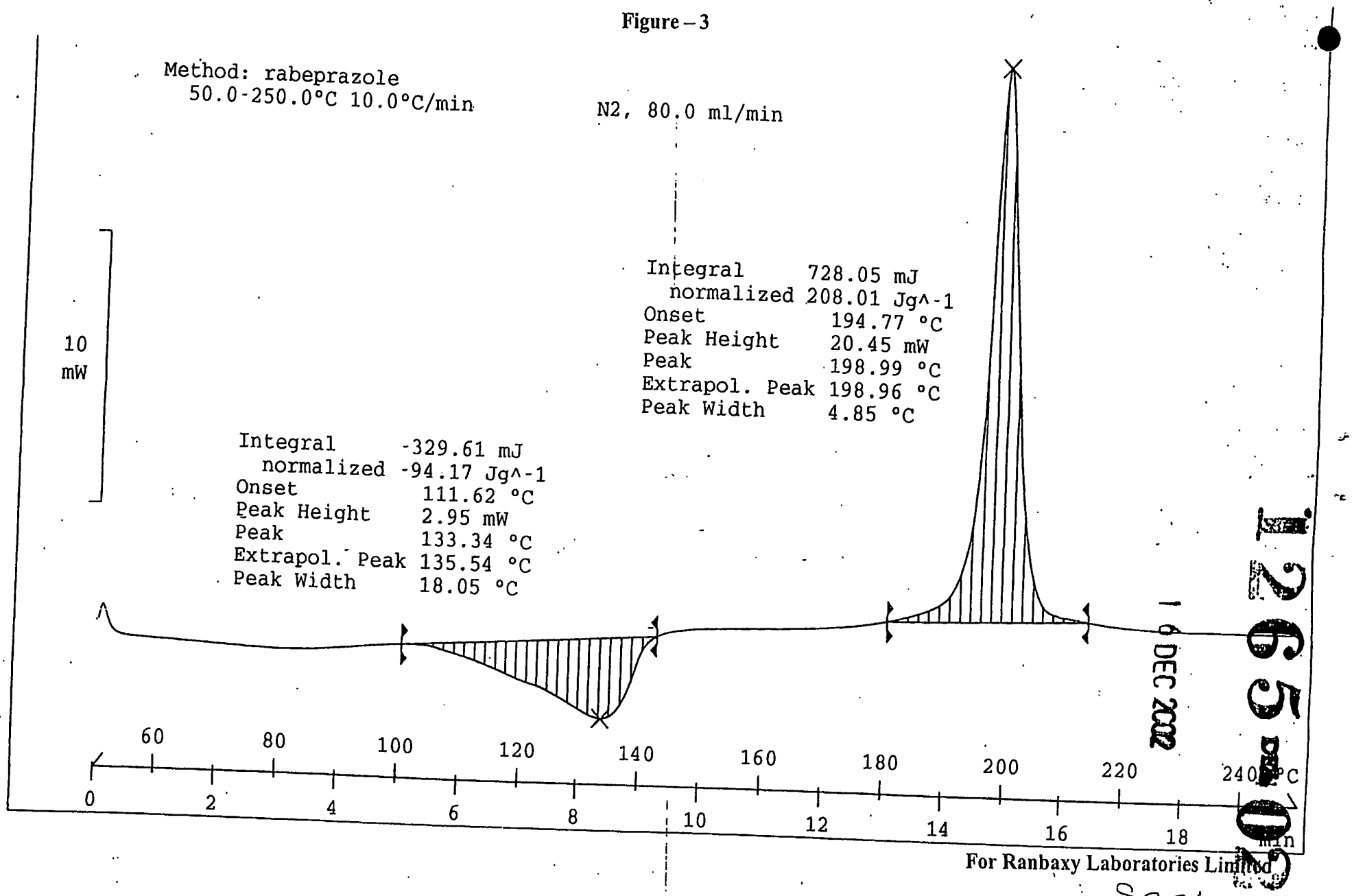
Figure – 1



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

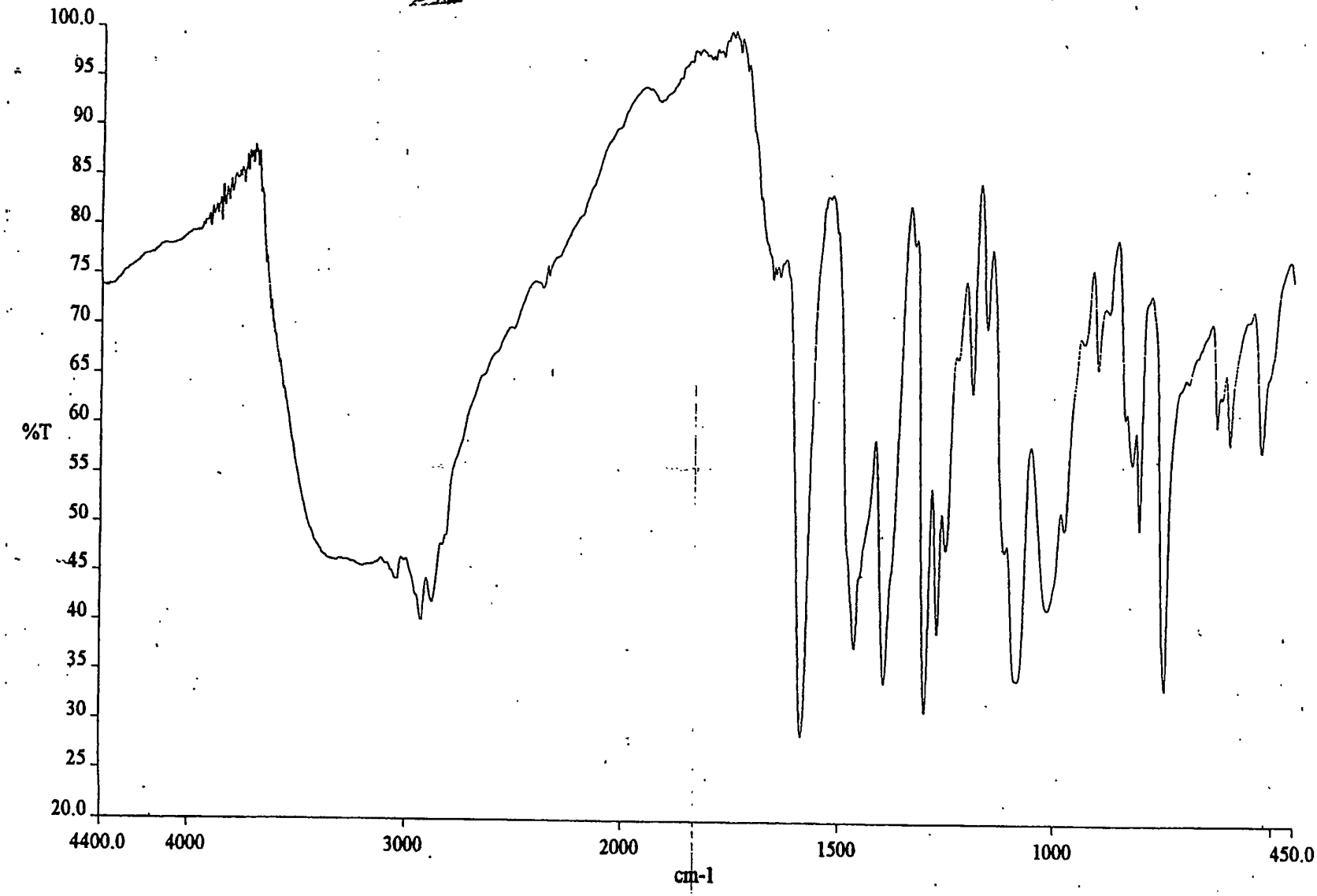
Figure – 3



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Figure – 5



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